PART I

Anatomy, pathophysiology, and electrophysiologic basis of atrial fibrillation

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CHAPTER 1

The morphology and development of the atrial chambers, with particular regard to atrial fibrillation

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Introduction

In a previous review of the structure of the atrial chambers [1], we drew attention to the fact that, during the period 1996 through 2000, a search using the online facilities of the National Library of Medicine in the United States of America revealed 2695 articles on atrial arrhythmias, a threefold increase compared to the previous 5-year period. When the search was addressed specifically to atrial fibrillation, the number of hits was appreciably higher, at almost 5000 for the second period, albeit that this was less than a twofold increase. At that time, however, accounts of gross anatomy of the atrial chambers barely featured. We argued that this situation could be interpreted as indicating that all was known about the gross anatomy of the atrial chambers, but we went on to suggest that this was far from the case. Since that time, in the initial 5 years of the current century, our prognostications have proved well founded, since there has been an upsurge in interest not only in the structure of the atriums, but also in the location within the atrial musculature of potential arrhythmic substrates. These have sparked ongoing discussion with regard to the features permitting the histologic recognition of the so-called "specialized" tissues [2–6]. At the same time, the search for increased morphological knowledge by electrophysiologists has been accompanied by amazing improvements in diagnostic techniques, such that the atriums can now be reconstructed with remarkable accuracy. More importantly, the information can now be presented to the clinician in the context of the overall arrangement of the body [7]. This emphasizes the need for atrial structures to be described using attitudinally appropriate nomenclature [8], a need, which we have also done our best to champion [9], albeit still with relatively limited success. In this chapter, therefore, it is our task to provide the electrophysiologist, arrhythmologist, and cardiologist, with a review of atrial structure, emphasizing the relationship of the atriums to other structures within the thorax, the location of the components of the conduction system, and other potential arrhythmic substrates. We will also introduce the significant advances made in understanding the development of the atrial chambers [10], since this sheds considerable light on the location of the arrhythmic substrates, and also resolves some of the disputes concerning the nature of the musculature making up the pulmonary venous sleeves [3], now well recognized as significant in the genesis of atrial fibrillation [11].

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The relationship of the heart within the body

Over the centuries, the basis for description of all structures within the body has been the agreement that they should be described as seen in the individual standing upright and facing the observer, the so-called "anatomical position" (Plate 1.1). It is surprising that this convention has been followed for virtually all the systems of organs, muscles, and nerves, yet ignored for the heart. Thus, almost all anatomic texts concerned with human anatomy, and all texts of clinical cardiology, continue to use adjectives for description of the heart that are based on its position as seen when removed from the body, and stood on its apex, the so-called "Valentine" configuration (Plate 1.2). In the past, when diagnosis depended on auscultation, or even on echocardiographic interrogation, these deficiencies were of relatively little significance, although the inconsistency of blockage of the "posterior" interventricular coronary artery producing inferior myocardial infarction cannot have gone unnoticed. With the proliferation of interventional techniques, particularly as used by the cardiologist to cure arrhythmias, these discrepancies became more significant. The conventional approach was recognized as being less than perfect when the interventionist realized it was necessary to describe a catheter inserted via the inferior caval vein as tracking anteriorly, when all the watchers could see the structure moving superiorly in the fluoroscopic screen [8]. Since the turn of the century, with the introduction of tomographic techniques that give the clinician the ability to reconstruct the heart in three dimensions, and to do so in the context of the other thoracic contents, the need to adopt an attitudinally appropriate nomenclature has become the more pressing [12]. In this chapter, therefore, we will describe all parts of the heart, including the atrial chambers as seen in their context of the living thorax (Plate 1.3), using adjectives as dictated by the anatomical position (Plate 1.1).

The basic arrangement of the heart within the thorax

The heart is positioned within the mediastinum, with its own long axis orientated from the right shoulder toward the left hypochondrium (Plate 1.4a). In the normal individual, two thirds of the bulk of the cardiac mass is usually to the left, with one third to the right. The overall cardiac silhouette projects to the anterior surface of the chest in trapezoidal fashion. It is convenient to consider the trapezoid itself in terms of atrial and ventricular triangles, the two meeting at the planes of the atrioventricular and ventriculoarterial junctions (Plate 1.4b and 1.5a). The relationships of the cardiac valves guarding the junctions are then well seen when the atrial myocardium and arterial trunks are removed, and the ventricular base is examined from its atrial aspect (Plate 1.5b). This dissection emphasizes, first, that the right atrium is positioned anteriorly relative to its alleged left-sided counterpart, and second, that the aortic valve forms the centerpiece of the cardiac short axis, being wedged between the mitral and tricuspid valves (Plate 1.5b). Examination of the cardiac structures in so-called "four chamber" orientation then shows how the heart is composed of the atrial and ventricular muscle masses, these two masses meeting at the atrioventricular junctions. Apart from the bundle of His, they are insulated electrically one from the other by the fibrofatty tissue planes of the junctions (Plate 1.6).

Relationship of the heart to the thoracic structures

The heart lies within the middle component of the mediastinum, enclosed within its pericardial sac, which functions as the cardiac "seat belt." Other important structures, of course, are also to be found within the thorax, and recent experience has shown that the interventionist needs to be well aware of their precise relationships to the heart. The location of the oesophagus has long been recognized as of clinical significance, since in the days prior to the advent of tomographic diagnostic techniques, the barium swallow was regularly used as a means of recognizing left atrial enlargement. Now, with the availability of magnetic resonance imaging, we are able to display the precise relationship of the oesophagus to the atrial components (Figures 1.1 and 1.2). As the section in the sagittal plane shows (Figure 1.1), the oesophagus runs within the posterior mediastinum directly behind the left atrium.

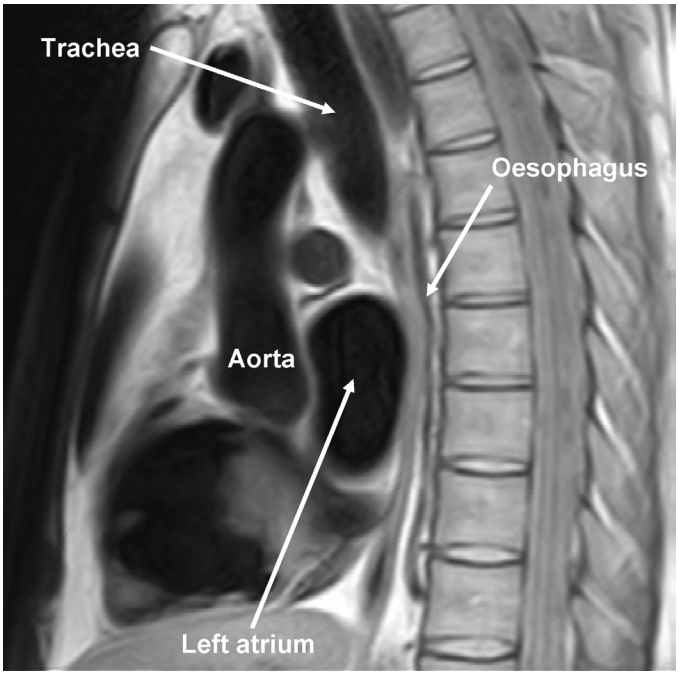

Figure 1.1 This magnetic resonance image is taken in the sagittal plane. It shows the intimate relationship between the oesophagus and the left atrium.

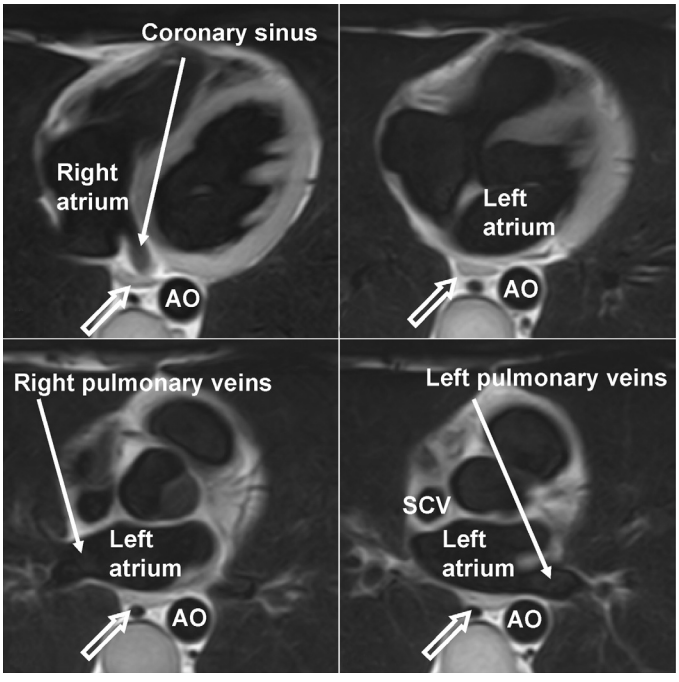

Figure 1.2 These resonance images, taken in the short axis of the body, show the relationship of the oesophagus (arrowed) to the atrial chambers at increasingly superior levels (a through d). AO, aorta.

Sections in the short axis then show that, just prior to its penetration through the diaphragm (Figure 1.2a), the oesophagus is directly related to the coronary sinus. When traced superiorly (Figure 1.2b–d) it comes into direct relationship with the posterior wall of the left atrium, running more-or-less along the middle of the chamber, albeit that reconstructions have shown that this relationship can vary with peristalsis even within the individual [7].

In addition to the oesophagus, and the aorta, albeit that the aorta is relatively distant from the atrial chambers (Figure 1.2), recent experience has shown that the interventionist also needs to take note of the relationship of the phrenic nerves as they pass through the thorax to innervate the diaphragm. In an elegant anatomic study, Sanchez-Quintana and colleagues [13] showed that the right phrenic nerve is intimately related to both the superior caval vein and the right pulmonary veins, running within millimeters of the lumens of these veins, whereas the left phrenic nerve was relatively safely located relative to the atrial chambers, albeit potentially at risk during implantation of leads into the great cardiac and obtuse marginal veins (Plate 1.7).

The phrenic nerves course through the mediastinum running anteriorly relative to the pulmonary hilums. Equally important are the vagus nerves, which extend through the mediastinum on both sides directly posterior to the hilums. These structures must also be at risk when ablations are carried out in the pulmonary venous orifices. The vagus nerves, along with the sympathetic chains, contribute numerous branches to the posterior cardiac plexus, which is intimately related to the left atrium and the interatrial groove. Thus far, the nerves have received relatively little attention, and a detailed account of their distribution is beyond the scope of this chapter, but it is likely that, in the near future, they will receive appreciably more attention [14].

The atrial components

Each of the atrial chambers is made up of comparable parts, albeit that the shape, orientation, and contribution of each component differ markedly between the two chambers. The basic components are the body, the appendage, the venous component, the vestibule, and the septum. Both the body and the appendage differentiate as working myocardium from the primary venous part of the linear heart tube. The body is placed in its larger part in the left atrium, with only a small part persisting in the right atrium between the venous component and the septum. We know, however, that the body forms a significant part of the left atrium, since this chamber retains a significant volume in the absence of its venous component, as seen in the congenital malformation of totally anomalous pulmonary venous connection (Plate 1.8). The two appendages also take their origin from the body, ballooning anteriorly during early development. Eventually, however, they come to form almost the entirety of the anterior wall of the right atrium, and a tubular extension from the body of the left atrium, both as anatomically discrete structures (Plate 1.9 and 1.10). Thus, the walls of the appendages are readily distinguished from the remaining atrial walls because of their pectinated appearance (Plate 1.9). The venous components are positioned posteriorly within both atriums. The venous sinus of the right atrium, derived from the initial bilaterally symmetrical systemic venous tributaries, receives the superior and inferior caval veins at its roof and floor, with the coronary sinus returning most of the venous drainage from the heart itself to the right atrium (Plate 1.9a). The venous component of the left atrium, a new developmental component, eventually receives one pulmonary vein at each of its four corners, and forms the roof of the left atrium, albeit with a degree of off-setting of the venous orifices (Plate 1.9b). The vestibules are the smooth atrial walls leading into, and attached at, the orifices of the atrioventricular valves (Plate 1.6 and 1.9). They are derived from the initial musculature of the atrioventricular canal. On the right side, the smooth vestibule is separated from the venous sinus throughout the extent of the atrioventricular junction by the pectinate muscles of the right appendage (Plate 1.9a). On the left side, in contrast, the smooth vestibule is confluent with the smooth walls of the pulmonary venous component and the body, the pectinate muscles being confined within the tubular appendage (Plate 1.9b). The septum is the wall

separating the cavities of the two chambers (Plate 1.11). It is made up largely of the fibrous floor of the oval fossa, the fossa itself representing the site of embryonic interatrial communication. The larger parts of the superior, anterior, and posterior margins of the fossa are formed by infoldings of the atrial walls. It is only the anteroinferior rim, leading to the vestibule in the environs of the triangle of Koch (see below), that can be removed, along with the floor of the fossa, so as to create a direct communication between the atriums without encroaching on extracardiac space [15].

Description of the atriums

As will have become evident from all our discussions thus far, when the atriums are considered in the setting of the body, which is the only realistic way for the cardiologist to approach atrial morphology, the terms "right" and "left" are inappropriate for positional description. In reality, the right atrium is the anterior atrium, with hardly anything of the left atrium, other than the tip of its appendage, being visible when the cardiac chambers are projected onto the cardiac silhouette as seen in the frontal projection (Plate 1.4a). It is unlikely, however, that we will ever describe the atriums as being the anterior and posterior chambers. In the normal heart, it would be more appropriate to describe them as the systemic and pulmonary venous atriums, but even this convention would prove lacking when the heart is congenitally malformed (Plate 1.8). The better way of describing the two chambers, therefore, is to recognize them as being morphologically right and morphologically left, this convention holding good even when the chambers are mirror-imaged in the setting of congenital cardiac disease. It is the structure of the appendages that best distinguishes between the two atriums, this feature holding good even when the heart is grossly malformed as in the setting of visceral heterotaxy. Indeed, in this setting, careful examination of the extent of the pectinate muscles shows that the atrial chambers possess either two right appendages, or two left appendages, and hence are well described as having isomerism of the morphologically right or left atrial appendages [16]. In the setting of the normal heart, or the hearts in patients with atrial arrhythmias, the important point is to appreciate that the atrial cavities are located more-or-less front to back. The atrial septum has a double oblique orientation, running posteriorly to anteriorly when traced from right to left, and at the same time, extending from anterior to posterior when traced from head to foot (Figure 1.2).

Positional arrangement of the components of the right atrium

In the right atrium, as their names suggest, the superior and inferior caval veins enter the roof and the floor of the systemic venous component, this part of the atrium being posterior to the extensive appendage. It is often thought that the appendage is no more than the triangular tip of the chamber abutting on the aorta (Plate 1.10). As is shown by the cast, nonetheless, the pectinated wall forms virtually the entirety of the front surface of the chamber (Plate 1.9a). When viewed from above, the pectinate muscles are seen to circle round the entirety of the vestibule of the tricuspid valve (Plate 1.12). Indeed, the muscles spill over and encroach on the diverticulum found beneath the coronary sinus (Plate 1.13 and 1.14), often described as the sub-Eustachian sinus. When the heart is positioned as it lies within the body, because this diverticulum is beneath the mouth of the coronary sinus, it is more appropriately described as being sub-Thebesian. The Eustachian and Thebesian valves, remnants of the right valve of the embryonic venous sinus [17], are found at the right boundary of the definitive systemic venous sinus, albeit being variably developed in different hearts. When extensive, they can become aneurysmal, particularly the Eustachian valve, and can form windsocks, which in extreme cases, can extend through the tricuspid valve and block the subpulmonary outflow tract.

More usually, the valves persist only as fibrous folds related to the openings of the inferior caval vein and the coronary sinus (Plate 1.14). It is then the commissure between the valves which is of more significance. This fibrous structure buries itself within the muscular posterior wall of the right atrium between the orifice of the coronary sinus and the depression formed by the oval fossa. This muscular area is known as the sinus septum, or the

Eustachian ridge. It is the fold between the walls of the coronary sinus, running in the left atrioventricular groove, and the margins of the oval fossa. The tendinous continuation of the fused venous valves extends throughout this musculature, burying itself in the anteroinferior rim of the atrial septum, and running anteriorly and superiorly to terminate in the so-called central fibrous body (Plate 1.14). We will return to discuss the central fibrous body when considering the location of the atrioventricular node and the bundle of His.

If we redirect our attention now to the appendage and the systemic venous sinus, an important groove is seen externally which marks the boundary between the two components. This is the terminal groove, or "sulcus terminalis." The superior extent of this groove is the crest of the atrial appendage, with the sinus node found subepicardially within the groove just inferior to this crest (Plate 1.15). Across the crest, the terminal groove becomes continuous with the anterior interatrial groove. Internally, the terminal groove corresponds with the location of the terminal crest, this being the prominent muscular bundle that forms the boundary between the appendage and the systemic venous sinus. The pectinate muscles extend like the teeth of a comb from the terminal crest to reach anteriorly as far as the smooth vestibule surrounding the tricuspid valvar orifice. In the anterior wall, the larger pectinate muscles are arranged nearly in parallel fashion, with thin branches in between, leaving areas of very thin atrial wall (Plate 1.13). Superiorly, at the tip of the appendage, the pectinate muscles lose their parallel arrangement. The terminal crest sweeps like a twisted "C," originating from the septal wall, passes anterior to the orifice of the superior caval vein, descends posteriorly and laterally, before turning anteriorly to skirt the right side of the orifice of the inferior caval vein. Close to its origin, the terminal crest is joined by a prominent bundle, the sagittal bundle, or "septum spurium," which extends anterolaterally toward the tip of the appendage. When traced inferiorly, the crest continues to form the boundary between the appendage and the systemic venous sinus, terminating in the region of the coronary sinus, where pectinate muscles continue to extend into the sub-Thebesian sinus. The inferior margin of the crest is of particular significance in the setting of atrial arrhythmias, since this is part of the so-called cavo-tricuspid isthmus (Plate 1.14). This inferior isthmus is an extensive and complex structure, possessing posterior, middle, and anterior components. The posterior part is pectinated. The middle part is the thinnest, incorporating the floor of the sub-Thebesian sinus, while the anterior part is smooth, representing the vestibule of the tricuspid valve (Plate 1.16). The vestibular part of the inferior isthmus is itself confluent with a second area of crucial significance to the arrhythmologist. This is the septal isthmus, the area between the mouth of the coronary sinus and the hingeline of the septal leaflet of the tricuspid valve (Plate 1.14). As we will see, this area harbors the so-called "slow pathway" into the atrioventricular node, albeit that the precise anatomic substrate for this pathway has still to be determined. Both the septal isthmus and the anterior part of the cavo-tricuspid isthmus are part of the vestibule of the right atrium, this being the smooth-walled component of atrial musculature that inserts into the full circumference of the orifice of the tricuspid valve, apart from the small area occupied by the membranous septum, this being part of the central fibrous body (Plate 1.14).

The final atrial component, the septum, forms the posterior wall of the right atrium, albeit that the septum itself is not nearly as extensive as is often thought. This statement requires a degree of explanation. From the perspective of the anatomist, we take the stance that a septal structure is that part of the walls of the heart that can be removed without encroaching on extracardiac space. In this way, we distinguish true partitions between adjacent chambers from folds or sandwiches [15]. When considered in this way, as we have already shown (Plate 1.11), the so-called "septum secundum" is no more than the superior interatrial fold, representing for the most part the deep infolding between the connections of the caval veins to the right atrium, and the right pulmonary veins to the left atrium. The anterior and superior border of the oval fossa is related directly to the aortic root (Plate 1.10). This anatomic feature is also of major significance to the interventionist, since the wall in this area often has crevices that can be mistaken for the space between the flap valve and the rim of the fossa itself. The interventionist seeking to achieve septal puncture may sometimes locate the

perforating device in one of the crevices rather than within the oval fossa. It is then easy, but regrettable, to puncture the aortic root rather than to pass into the left atrium (Plate 1.17).

The Eustachian ridge itself, running between the orifice of the coronary sinus and the inferior margin of the fossa, becomes continuous with the anteroinferior margin, then forming the other truly septal component of the posterior wall (Plate 1.11). In the past, we were of the opinion that the anterior continuation of this buttress formed part of an atrioventricular muscular septum. We now know that, although this muscular wall does indeed interpose between the cavities of the right atrium and the left atrium, it is a sandwich rather than a true septum. This is because an extension from the inferior atrioventricular groove runs between the right atrial and left ventricular musculatures in this area, carrying the artery to the atrioventricular node (Plate 1.18). The atrial part of this musculature, nonetheless, is crucially important to the arrhythmologist, since it contains on its inferior surface the compact atrioventricular node.

We have made no mention thus far of the location of a body within the right atrium. The part of the myocardium derived from the primary atrium is squeezed between the septum and the leftward margin of the systemic venous sinus. It is not possible in the postnatal heart, however, to recognize any anatomic boundaries in this area distinguishing the origin of the different myocardial components, as is possible at the rightward margin, which is marked by the terminal crest and the remnants of the right venous valve. As we will discuss later, it is possible to recognize such a boundary in the developing heart, which is formed by the left venous valve. It is the "septo-valvar space" between the left venous valve and the septum that represents the body of the right atrium, this being the part from which, during development, the appendage has ballooned prior to incorporation of the systemic venous sinus.

Positional relationships of the components of the left atrium

As with the right atrium, the left atrium is made up of the appendage, the vestibule, the pulmonary venous component, and the left aspect of the septum. The left atrium also retains the larger part of the atrial body derived from the primary atrium, albeit that there are no anatomic boundaries that show the different parts of the smooth-walled atrium derived from the various developmental components. The left atrium also lacks a terminal crest, or "crista terminalis," so there is no groove between appendage and the smooth-walled part of the atrium such as seen on the right side. The appendage is readily recognized, nonetheless, because of its tubular shape, and its narrow junction with the remainder of the left atrium (Plate 1.19). It is positioned anterosuperiorly and leftward relative to the body of the atrium (Plate 1.20). The pulmonary venous component is shaped like a pillow, with the pulmonary veins entering the four corners of the superoposterior aspect. The left veins enter the atrium more superiorly than the right veins, albeit that this relationship is grossly distorted in Plate 1.15. The true relationship is shown by reconstructions made from computed tomographic or magnetic resonance images (Plate 1.21). Variation in the number of veins entering the human left atrium is not uncommon. Sometimes two veins of one, or both, sides unite prior to entering the atrium. In others, an additional vein is found, more frequently on the right side. In a recent description based on tomographic images, emphasis was placed on recognizing a so-called "roof" vein [18]. It should also be noted that five or six pulmonary venous orifices are described for the canine heart [1], although some veins become confluent just before entering the left atrium. There are two veins, one on each side, in the porcine heart. In the murine heart, in contrast, there is but a solitary vein entering the left atrium [19]. These differences between species need to be taken into account when judging the significance of experimental results to arrhythmias as seen in the human. In our limited experience in assessing variations in the human, it is more common to find the right upper veins joining to enter as one vein, with the orifice located slightly superiorly to the common left upper venous orifice. The septal aspect of the left atrium, forming the anterior wall of the chamber, is usually marked by shallow and irregular pits on the flap valve of the oval fossa. A crescent marks the free edge of the flap valve (Plate 1.19). It is through this margin that a probe or catheter can be pushed obliquely and anterosuperiorly along the fossal surface on the right

side to enter the left atrium. Indeed, in up to one third of the normal population, there is no anatomic fusion between the flap valve and the left side of the margins of the oval fossa [20]. Such failure of fusion produces a probe-patent oval foramen, now known to be a harbinger for cryptogenic stroke [21], and perhaps even a cause of migraine [22]. As we have stressed when discussing the right atrium, the anterior rims of the oval fossa can themselves exhibit holes or crevices. The walls are also very thin close to this point, increasing the risk of exiting the heart during attempted septal puncture. As with the right atrium, the vestibular musculature inserts into the left atrioventricular junction around the margins of the annulus of the mitral valve. Unlike the right side, however, the left-sided vestibule is a complete ring of muscle.

An important structure related to the left atrium is the coronary sinus, albeit that this venous channel, as already discussed opens into the systemic venous sinus of the right atrium. In the past, we thought that the wall of the sinus was directly continuous with that of the posterior vestibular of the left atrium, the two representing a "party wall." We now know that this is not the case (Plate 1.20), the elegant study of Chauvin and colleagues [23] proving that the walls of the sinus are discrete entities, albeit with muscular bridges running from the wall of the sinus to the left atrial musculature. In the normal individual, the coronary sinus, representing the remnant of the left sinus horn, does no more than serve as a conduit to channel most of the coronary venous return to the right atrium. The remaining part of the initially symmetrical left cardinal vein is then seen as the oblique vein of the left atrium, the site of this venous channel being taken by some as marking the junction of the coronary sinus and the great cardiac vein (Plate 1.22). Others use the location of the prominent valve within the venous conduit, the valve of Vieussens, as the boundary between the great cardiac vein and the sinus. As can be seen from the cast shown in Plate 1.22, this junction is somewhat arbitrary, since the venous conduit continues as an uninterrupted channel throughout the left atrioventricular groove. In the adult heart, the walls of the funnel-shaped venous channel are located approximately 1–1.5 cm proximal to the internal plane corresponding to the mitral valvar orifice [24].

The muscular walls and muscular venous sleeves

The atrial mass is an integral muscular whole, albeit with walls of varying thickness and complexity, and with relatively limited connections between the two atriums. The varying thickness of the walls is particularly well seen in the right atrium. The most prominent bundles are the terminal crest, the Eustachian ridge, the rim of the oval fossa, the pectinate muscles, and the tricuspid vestibule. When attention is given to the epicardial aspect of the terminal crest at the crest of the right atrial appendage, then a prominent band of muscular aggregates can be traced from the superior cavoatrial junction leftward to become the superficial fibers of the left atrium. Best known as Bachmann's bundle, this band crosses the anterior interatrial groove (Plate 1.23). As initially emphasized by Bachmann himself [25], the bundle is not ensheathed by fibrous tissue, and is of varying widths and thicknesses in different hearts. It lacks distinct margins, and it is the parallel arrangement of myofibers that almost certainly confer upon it the state of the superhighway for interatrial conduction. There are then other important interatrial bundles that cross the superior or posterior parts of the interatrial groove, and still others that connect the wall of the coronary sinus to the left atrium (Plate 1.24). The floor of the oval fossa, however, is made up largely of fibrous tissue in the adult human heart, and is therefore electrically inert. The anteroinferior margin of the oval fossa, nonetheless, is a true septal structure, so this area also constitutes an electrical bridge between the atriums. In all these prominent muscle bundles, it is the alignment of the long axis of the myocytes that sets the scene for preferential conduction, since as we will emphasize shortly, there are no discrete insulated muscular tracts running through the atrial walls, either between the sinus and atrioventricular nodes, or between the atriums.

Being mainly smooth, the left atrial wall gives the impression of muscular homogeneity. Detailed dissections through its full thickness, however, reveal it to be composed of overlapping broad bands of myofibers. These run in different directions, but the layers again are not insulated one from the other by fibrous sheaths. The superficial myofibers are

mostly orientated parallel to the atrioventricular junction, while the deeper fibers run obliquely or perpendicularly to the junction. The superior wall, however, is composed mainly of the perpendicular or oblique fibers of the septopulmonary bundle (Plate 1.24).

The recording of electrical activity in the thoracic veins, and the ablation technique developed by Haissaguerre and his colleagues for treating paroxysmal atrial fibrillation [11], have focused attention on the muscular sleeves surrounding the proximal parts of the both the systemic and the pulmonary veins. Encircling the veins to varying extents, the sleeves are continuations of atrial musculature along the epicardial aspect of the venous wall [6]. They tend to be thicker and more complete near the cavoatrial or pulmonary–atrial junctions, but taper and fragment as they move further away from the junction. When considering the pulmonary veins, the upper veins tend to have longer sleeves than the lower ones, which are often devoid of sleeves (Plate 1.25). It is no coincidence that ectopic focuses are most commonly found in the superior veins. Although claims have been made for the existence of "specialized" cells in the human heart [5], we have found no evidence demonstrating specialization of the cells (Plate 1.26) [6, 26]. It is almost certainly the nonuniform anisotropic pattern of the myocytes in their supporting fibrous matrix that sets the scene for focal activity (Plate 1.27). Muscular sleeves are seldom well-developed around the inferior caval vein. In contrast, the superior caval vein usually has a discernible cuff of atrial muscle extending some distance from the cavoatrial junction. The sleeves around the caval veins, irrespective of their length, when judged histologically are again made up exclusively of working myocardium. Some have suggested that the oblique vein of the left atrium might also be a site of arrhythmogenesis. We find this unlikely, since the vein is a small structure, representing no more than the remnant of the left cardinal vein.

The location of the specialized atrial myocardium

As we have already demonstrated and discussed, the larger parts of the atrial walls are made up of ordinary working myocytes. The myocytes themselves are aggregated within a supporting matrix of fibrous tissue, the parallel alignment of these aggregates favoring preferential conduction along the direction of their long axis, the overall arrangement being one of nonuniform anisotropy [27]. Within the overall structure of the atrial walls, nonetheless, certain parts of the myocardium show so-called histologically "specialized" characteristics. One of these areas, the sinus node, is known to be the generator of the cardiac impulse [28]. Another area, the atrioventricular node and its zones of transitional cells, is the atrial component of the solitary axis of muscular tissue, which joins the atrial and ventricular muscle masses [29]. At various times, and in various places, however, multiple investigators have suggested that other parts of the atrial myocardium are histologically specialized. For quite some time, these suggestions focused on the presence or absence of muscular "tracts" extending between the sinus and atrioventricular nodes [30]. More recently, the suggestions have centered on the possibility that additional areas of "specialized" tissue could form the focus for abnormal atrial rhythmicity [2, 3, 5]. All these potential controversies, however, could have been avoided had the protagonists for histological specialization followed the criteria suggested by the great German pathologists, Aschoff [31] and Mönckeberg [32]. The need for these criteria had appeared when Thorel, another German investigator, was the first to suggest that the atrial myocardium interposed between the newly discovered sinus and atrioventricular nodes was histologically specialized [33]. Aschoff [31], and Mönckeberg [32], in presentation to a meeting of the German Society of Pathology, held in Marburg in 1910, pointed out that the careful studies of Tawara [29] provided the basis for appreciating the histological essence of "specialization." In a truly epochal study, first published in 1906 as a monograph in German, but now available in an excellent English translation [29], Tawara had shown that the axis for atrioventricular conduction took its origin from the "knoten," or atrioventricular node. The axis then penetrated the insulating tissues separating the atrial and ventricular muscle masses, and then continued to be insulated from the ventricular myocardium as the branches of the atrioventricular bundle, enclosed in fibrous sheaths, coursed on either side of the muscular ventricular

septum, merging with the ventricular myocardial mass only when they had reached the ventricular apexes. Taking this account as their example, Aschoff and Mönckeberg suggested that specialized tracts within the walls of the heart should, first, be composed of cells which are histologically distinct from their neighboring walls of working myocardium, second, should be enclosed by fibrous sheaths, and third, should be followed from section to section in blocks of myocardium prepared using the technique of serial sectioning. The paradigm for such a tract is the right bundle branch (Plate 1.28). When examining the atrial myocardium histologically, then no structures are to be found which satisfy all three of the criteria suggested by Mönckeberg [32] and Aschoff [31], criteria which still retain their currency, and have yet to be superceded by better "rules" for recognition of histologically specialized tissue. Thus, when examined in the light of the existing rules, it is now established beyond any doubt that insulated tracts of atrial myocardium do not exist within the atrial walls. As we will see, there are areas of the walls that show differences one from the other, but none which satisfy the criteria for existence as tracts comparable to the ventricular bundle branches.

When we examine the histological arrangement of the sinus and atrioventricular nodes, structures of which the functions are no longer in doubt, then we find that they satisfy only two of the three criteria established by Aschoff [31] and Mönckeberg [32]. These nodes are histologically discrete from the adjacent working myocardium, and can be followed from section to section in serially sectioned histological blocks. The cells of the nodes, however, are not insulated from the adjacent myocardium. Indeed, it would destroy their purpose where they thus insulated. The purpose of the sinus node (Plate 1.29) is to generate the cardiac impulse. The pacemaking cells, therefore, need to be in electrical contact with the adjacent working myocardial cells. This transition from the nodal tissue to working atrial myocardium occurs at all borders of the node where there is contact with the atrial walls. But there are no "tracts" emanating from the node other than the tail extending for variable distance down the terminal groove. Similarly, the atrial myocardial cells adjacent to the atrioventricular node change their histological structure, becoming isolated and elongated, and recognizable as transitional cells (Plate 1.30). These transitional cells themselves then undergo further transitions, grouping themselves together to become the compact node, which is then engulfed by the fibrous tissue of the central fibrous body to become the bundle of His (Plate 1.30). When we apply these two criteria, histological differentiation and the ability to follow structures through serial sections, we then find other areas of atrial myocardium that are histologically specialized (Plate 1.31). These are the node-like structures found at various points within the vestibule of the tricuspid valve. Originally discovered by Kent in 1893 [34], and illustrated in 1913 [35], Kent wrongly assumed that the nodes extended across the insulating fibrofatty groove between the right atrium and the right ventricle. As we showed subsequently [36], the structures, which truly resemble a miniature atrioventricular node (Plate 1.31), are located within the insertions of the right atrial vestibular into the orifice of the tricuspid valve. As we will show below, they are the remnants of a more extensive ring of primary myocardium that initially surrounds the atrioventricular junction and embryonic interventricular foramen, and which also becomes incorporated into the developing right atrial vestibule. In the normal heart, the nodal remnants make no contact with the ventricular myocardium. It has been suggested that the part of the original ring in the septal isthmus forms the slow pathway into the atrioventricular node [37], albeit that not all patients with atrioventricular nodal tachycardia possess such histologically identifiable structures [38]. The node-like structures, nonetheless, can function as part of electrical atrioventricular connections, either in the so-called "Mahaim" type of preexcitation [39], or in congenitally malformed hearts such as congenitally corrected transposition [40]. Other than the sinus and atrioventricular nodes, and the remnants of specialized tissue known as the atrioventricular ring tissue [36], and despite claims to the contrary [2, 3, 5], there are no other areas of the walls of the right or left atrium, including the pulmonary venous sleeves, which are histologically specialized when set against the criteria established by Aschoff [31] and Mönckeberg [32] in 1910.

The location of the cardiac nodes

It is important for the clinician, and particularly the electrophysiologist, to be able to identify with accuracy the locations of the sinus and atrioventricular nodes within the walls of the right atrium. The sinus node is a small, cigar-shaped, structure set immediately subepicardially within the terminal groove, its body being wedged between the wall of the superior caval vein and the musculature of the terminal crest. In an earlier study [41], we found that, in addition to a tail extending for various distances down the terminal groove toward the orifice of the inferior caval vein, in one tenth of the specimens studied, the node also extended in horseshoe fashion across the crest of the right atrial appendage. In a subsequent study of adult human hearts [42], however, we did not encounter any horseshoe nodes, all examples lying laterally within the terminal groove (Plate 1.15). The nodal cells themselves are immediately subepicardial, and make short transitions with the atrial myocardium throughout the boundary between the node and the terminal crest (Plate 1.29). It is noteworthy that, in most individuals, a prominent artery courses through the middle of the node, although the specific arrangement varies from heart to heart [43]. This artery to the sinus node is an early branch of the right coronary artery in just over half individuals, taking origin from the initial course of the circumflex artery in just under half, with rare individuals exhibiting lateral origin from more distal parts of the right or circumflex arteries. This variation in arterial supply is likely to be of greater significance to the cardiac surgeon than to the electrophysiologist [43].

As we have emphasized, there are no insulated tracts emanating from the sinus node and coursing either into the left atrium, or toward the atrioventricular node [44]. As was shown by Bachmann himself [25], it is the parallel arrangement of the aggregates of myocytes that is responsible for preferential conduction along the prominent thick atrial muscular bundles. Amongst these, the most important are Bachmann's bundle itself (Plate 1.23), the margins of the oval foramen, and the vestibule of the tricuspid valve (Plate 1.14). It is the latter muscular structures, which make up the approaches to the atrioventricular node, but not forgetting that, as an interatrial structure, the node is also in electrical contact with the left atrial side of the septum (Plate 1.30). The anatomical landmark to the location of the atrioventricular node is the triangle of Koch. This triangular area is delineated on the atrial side by the course of the tendon of Todaro through the Eustachian ridge to the central fibrous body, and on the ventricular side by the hingeline of the septal leaflet of the tricuspid valve (Plate 1.14). These sloping borders meet superiorly at the apex of the triangle, formed by the central fibrous body. The base of the triangle, containing the mouth of the coronary sinus, is the cavo-tricuspid isthmus. The atrial wall of this triangle is a thin layer of myocardium that is separated from the underlying ventricular myocardium by an extension from the fibrofatty atrioventricular groove. This groove is traversed by the artery to the atrioventricular node, which takes its origin from the dominant coronary artery, this being the right coronary artery in nine tenths of the population. The artery courses superiorly, entering the compact node, which is located in the union of the right and left atrial walls at the apex of the triangle (Plate 1.30). When traced further superiorly, the compact node itself then becomes engulfed by the tissues of the central fibrous body. This body, the strongest part of the cardiac skeleton, is formed from the union of the right fibrous trigone, the rightward end of the region of continuity between the leaflets of the aortic and mitral valves, and the membranous part of the ventricular septum. This arrangement is best appreciated from the aspect of the left ventricular outflow tract (Plate 1.32). In the setting of atrial fibrillation, the interventionist is likely to wish to know the site of penetration of the conduction axis so as to ablate it. As can be appreciated from Plate 1.14, 1.30, and 1.32, this can best be achieved from either the right side, or through the subaortic outflow tract. From the right side, the landmark to penetration of the bundle of His is the apex of the triangle of Koch. In the subaortic outflow tract, the bundle emerges onto the crest of the muscular ventricular septum immediately beneath the zone of apposition between the right coronary and noncoronary leaflets of the aortic valve. The node can also be approached from the left atrium, but is

then much deeper within the atrial septum (Plate 1.30). The landmark from the left atrial side is the atrial vestibule immediately adjacent to the septal end of the zone of apposition between the two leaflets of the mitral valve [43]. Although of less immediate significance to the treatment of atrial fibrillation, the interventionist also needs to be aware of the sites of the so-called "slow" and "fast" pathways into the atrioventricular node. As we have already discussed, the slow pathway is located within the septal isthmus (Plate 1.11), albeit that the anatomical substrate has still to be determined with certainty [37, 38]. The fast pathway is located in the anterosuperior rim of the oval fossa, immediately superior to the location of the tendon of Todaro. Again, the anatomic substrate of this structure has yet to be established, but our bias remains that conduction through both pathways into the node is conditioned by the variability in alignment of the myocardial aggregates within the atrial walls [37].

Substrates for abnormal atrial rhythmogenicity

We have emphasized in the preceding paragraphs that there are no insulated tracts of atrial myocardium extending between the sinus and atrioventricular nodes, with preferential conduction between the nodes achieved because of the morphologic arrangement of the working myocardial cells [27]. This does not mean, however, that the cells in these areas have never shown differences from the remainder of the atrial walls. Recognition of this fact is the more significant because, although not recognizable anatomically in the postnatal heart as conduction tissues, the cells forming the internodal atrial area are known to be the substrate for focal atrial tachycardias [45]. The features of these cells that differentiate them from the remainder of the atrial walls cannot be determined on the basis of classical histology. The features, nonetheless, have been clarified by recent findings in the fields of molecular biology and immunohistochemistry, which also impact on the nature of the myocardial sleeves surrounding the pulmonary veins. Taken together, the findings show the need to broaden our recognition of the conduction system based exclusively on histological criteria, considering also the potential substrates for abnormal electrical events as seen within the heart as it develops.

In the postnatal human heart, each heartbeat is generated by a wave of depolarizing impulses originating from the sinus node. Having traversed the working atrial myocardium, and activating it to contract, the impulse is collected in the atrioventricular node, where it is slowed, before being conducted rapidly through the histologically specialized and insulated fibers of the ventricular conduction axis to the ramifications of the peripheral ventricular conduction system, where it finally activates the ventricular working myocardium to contract. This sequence of electrical myocardial activation is registered in the electrocardiogram. The working myocardium of the cardiac chambers themselves, in addition to the anatomic components of the conduction system, is necessary to produce a normal electrocardiogram, as is the insulation found at the atrioventricular junctions at all points other than the penetration of the bundle of His. Although essential components of the overall system, neither the working myocardial elements, nor the fibrofatty elements providing electrical insulation, are considered traditionally as parts of the anatomic conduction system.

This distinction between "specialized" and "working" elements is the more pertinent to the arrangements of the hearts found in lower vertebrates, and to the morphology seen in the hearts of mammals and birds during their development. In lower vertebrates, and in mammalian and avian embryos early in their development, it is possible to record normal electrocardiograms. Yet neither in the hearts of fishes, nor early in the developing heart of birds and mammals, is it possible to recognize the morphologically discrete elements that we subsequently identify as conduction tissues using the definitions of Aschoff [31] and Mönckeberg [32]. The consecutive recordings of depolarizations of atrial and ventricular working myocardium, along with a period of atrioventricular delay, nonetheless, are a fundamental element of electrical patterning of the vertebrate heart. And the basis for development of this electrical design is the key to understanding the function of the components that generate and disseminate the impulse, irrespective of whether or not the components themselves are anatomically distinct.

In all species, the heart tube, when first formed, is simply a myocardial mantle enfolding a ventrally located endocardial tube. Within the walls of the tube at this stage, each myocyte is potentially a pacemaking cell, being inherently rhythmical, and poorly coupled to its neighbors because of a scarcity of gap junctions containing connexin45. Myocardium of this type can be dubbed "primary" myocardium [4, 46]. An electrocardiogram comparable to that seen in the postnatal heart, however, is not recorded until the larger part of the myocardium forming the walls of the atriums and ventricles is ballooned from this primary heart tube (Plate 1.33). This ballooning myocardium, therefore, can be considered secondary, or chamber, myocardium [4]. It is characterized electrically by its ability to conduct rapidly, containing gap junctions rich in both connexin40 and connexin43. The chamber myocardium also stains positively for atrial natriuretic factor. This permits its immunocytochemical distinction from the primary myocardium, which does not contain either atrial natriuretic factor, or connexin40 (Plate 1.34). As these secondary parts of the chambers are ballooned from the primary tube, the interposing areas of myocardium retain their primary characteristics, having high automaticity and conducting slowly. Indeed, small parts of the primary myocardium will retain these initial characteristics throughout development, eventually becoming the sinus and atrioventricular nodes, as will the other parts of the atrioventricular canal which persist as components of atrioventricular ring tissue [36] recognized using the criteria of Aschoff [31] and Mönckeberg [32]. We must ask, therefore, why all this primary myocardium does not persist and become histologically recognizable conduction tissues? This can be answered by recent findings concerning the role of transcription factors of the T-box family.

Transcription factors of the T-box family are essential to many of the processes needed for patterning of the vertebrate embryo [47]. Tbx5, for example, is known to be expressed in a caudocranial gradient along the heart tube. It is able to condition the appropriate development of the cardiac chambers, as well as the individual components of the anatomic conduction system. Haploinsufficiency of the gene produces not only septal defects, but also problems with conduction [48]. This particular transcription factor is also needed to activate the gene that encodes both atrial natriuretic factor and connexin40 [48, 49]. These are some of the proteins expressed in the chamber myocardium that balloons from the primary tube, but they are lacking from the areas of primary myocardium (Plate 1.34). Establishing the pattern of expression of Tbx5 itself, however, does not explain why the genes for atrial natriuretic factor and connexin40 are activated only in the chamber myocardium.

We now know that, concomitant with formation of the myocardium of the chambers, other genes of the Tbx family, initially Tbx2, and slightly later Tbx3, become expressed in the walls of the systemic venous tributaries, the atrioventricular canal, and the developing outflow tract [49], all these areas composed initially of primary myocardium. These latter genes are repressors of transcription [50]. In cooperation with Nkx2-5, they are able to repress the expression of the genes producing atrial natriuretic factor and connexin40. In this way, they permit the primary myocardium to persist in parts of the developing atriums, where it forms a corridor between the atrioventricular canal and the systemic venous tributaries (Plate 1.35). And it is at either end of this area that, eventually, we find the nodes of the anatomic conduction system.

In this respect, it is noteworthy that the original anatomic descriptions of Keith and Flack [28], as well as those subsequently made by Benninghoff [51], match almost seamlessly the patterns of expression for the T-box transcription factors and connexin40. The reconstruction shown in Plate 1.35, from a mouse heart at 9.5 days gestation, shows how the roof of the atrium, at this stage, consists of the rapidly expanding chamber myocardium. Its floor, in contrast, is primary myocardium, interposing between the eventual sites of formation of the cardiac nodes. With ongoing development, the entrances of the systemic venous tributaries, and part of septating atrioventricular canal, become incorporated within the developing right atrium, as does the intervening corridor of primary myocardium, from which the sinus node will be formed at one of its extremities, and the atrioventricular node at the other (Plate 1.35).

In this respect, Rentschler and coworkers [52], using as a molecular marker the reporter gene engrailed-LacZ, have shown that, in the mouse, all the components of the anatomically recognized cardiac conduction system, but in addition the internodal area along with the entire atrioventricular junctional area, are initially under the same transcriptional control. The mechanism of regulation, however, as yet remains undefined. The patterns noted during development for the expression of connexin45, nonetheless, display a remarkable similarity to those seen for Tbx2 and Tbx3, with all being expressed in the regions initially composed of primary myocardium.

Connexin45 is the first connexin to be detected in the embryonic heart tube, being first seen at 8.5 days of development in the mouse. It can subsequently be found in all the individually recognized components of the conduction system, and also in the terminal crest and the atrioventricular region, as well as in the myocardium of the developing outflow tract [53]. The presence of connexin45, therefore, serves to identify the initial location of the primary myocardium, its subsequent location in the anatomical conduction system, and its persistence in a number of associated areas.

If we combine this evidence that has emerged from the findings concerning the T-box transcription factors, engrailed-LacZ, and connexin45, it seems that parts of the walls of the developing atrial chambers are shielded from formation of secondary myocardium. In the postnatal heart, it is parts of these shielded areas that persist as the anatomically recognizable parts of the atrial portion of the conduction system. Other parts remain in vestigial form (Plate 1.36). Although we have been at pains to emphasize that atrial tracts analogous to the ventricular pathways for conduction do not exist, we do not seek to deny that a prominent region of the developing heart can be found along the terminal crest that expresses Tbx3, and which also runs between the definitive nodes. The markers used identify this area of the developing heart as being primary myocardium. In the postnatal human heart, it has become indistinguishable morphologically and histologically from the remainder of the right atrial myocardium.

All the molecular studies discussed above also show the atrioventricular region to be a distinct component of the atrial chambers, lacking as it does expression of connexin40, connexin43, and atrial natriuretic factor, but being positive for Tbx3. It is this atrioventricular region that forms the right and left atrial vestibules. In terms of their gross histology, these vestibules are indistinguishable, in their greater part, from the working myocardium of the remainder of the atrial chambers. A small part of the initially dorsal aspect of the region, of course, persists as the atrioventricular node. The remaining parts have reverted anatomically to a working phenotype, even though McGuire and coworkers showed that, when studied electrophysiologically, the entire region had nodal characteristics [54]. It is surely more than coincidence, therefore, that ectopic nodes are found in these areas in congenitally malformed hearts [40], and the specialized atrioventricular ring tissue is to be found in the right atrial vestibule even in the normal heart (Plate 1.31).

It is then also surely more than coincidence that focal tachycardias arising from the right atrium are far from randomly distributed, originating primarily along the long axis of the terminal crest, around the atrioventricular bundle, around the orifice of the coronary sinus, and around the vestibules of the mitral and tricuspid valves [45]. These are the precise areas identified anatomically and molecularly as representing the residue of the primary myocardium. We speculate, therefore, that these regions maintain their embryonic phenotype relatively long during development. Despite achieving a working anatomic phenotype in postnatal life, it is likely that their developmental heritage renders them prone to the generation of arrhythmias.

Finally, these molecular considerations can be extended to the sleeves of myocardium surrounding the pulmonary veins. We have already discussed the lack of evidence for histologic specialization of the myocytes making up the sleeves. From the stance of development, both the pulmonary and the systemic tributaries of the venous pole of the developing heart constitute a dynamic region, which is rapidly growing and remodeling [52]. The rapid changes occurring within the region are reflected in the expression of markers such as HNK1 [2, 3]. When considered in terms of the pattern of expression of atrial natriuretic factor and connexin40, however, the pulmonary myocardium is

negative for the first, and positive for the second, indicating that it is not primary myocardium. The myocardium surrounding the systemic tributaries, in contrast, is negative for both atrial natriuretic factor and connexin40, showing that it is primary in its origin. The pulmonary myocardium, therefore, is a new development not only in evolutionary, but also in embryonic terms [10]. There is no convincing evidence to support its anatomically specialized nature.

Etiological factors relating to atrial fibrillation

Although the focus of our chapter has been anatomic features pertinent to the treatment of patients with atrial fibrillation, thus far we have not discussed any morphologic features specific to such patients. This is because, to the best of our knowledge, studies comparing the atrial morphology of groups of patients with and without fibrillation are largely lacking. Studies have demonstrated an increase in fibrous tissue in the sinus nodes [55], and overall increase in the content of fibrous tissue within the dilated walls of the left atriums [56], albeit not always from patients with fibrillating hearts. We do not know with certainty, therefore, whether these changes cause the atriums to fibrillate, or whether, in the hearts that are fibrillating, the changes are the cause or the effect of the fibrillation. Similarly, studies of the pulmonary venous sleeves have largely been carried out on samples removed from patients with normal rather than fibrillating hearts. Thus, we now know much more about how fibrillation can be stopped by focal ablation in the pulmonary veins, or by compartmentation of the atriums using maze procedures, either surgically or by means of interventional catheterization, but we have yet to identify specific morphologic features precipitating the onset of fibrillation. There is much still to be learnt with regard to the structure and histology of the fibrillating heart.

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